AMENDMENTS TO THE SPECIFICATION

Please insert on page 1, before the heading "Field," the following paragraph:

This application is a continuation of application serial no. 09/471,349, filed December 23, 1999, which is abandoned.

Please replace the paragraph bridging pages 7 and 8 of the specification with the following amended paragraph:

To achieve the functional objective of an initially time-delayed PG activation kinetics a by hybrid SK derivatives, our design utilizes the fusion of selected regions of the FEBs of human fibronectin or its homologous sequences present in other proteins with SK (or its partially truncated forms) at strategically useful points so as to kinetically hinder the initial interaction of SK with PG necessary to form the 1:1 stoichiometric activator complex. It is known that of the 414 residues constituting native SK only the first 15 residues and the last 31 residues are expendable, with the resultant truncated polypeptide being nearly, as active as the native full-length protein in terms of PG activation ability (Young, K.C. et al., (1995) J. Biol. Chem. 270:29601-29606; Jackson KW, Malke H, Ferretti JJ, and Tang J (1986) Biochemistry 25:108-114~~Jackson, K. W,, and Tang, J. (1982) Biochemistry 21:6620~~). Further truncation at either end results in drastic decrease in the activity associated with the molecule (Malke, H., Roe, B., and Ferretti, J. J. (1987) In: Streptococcal Genetics. Ferretti, J. J., and Curtis, R. III [Ed.]Proc. American Society for Microbiology., Wash. D.C. p. 143). It has been demonstrated that SK interacts with PG through at least two major loci, mapped between residues 16-51 and 230-290 (Nihalani, D., Raghava, G. P. S., and Sahni, G., 1997, Prot. Sci. 6:1284), and probably also the

region in and around residues 331-332 (Lin, F. L., Oeun S., Houng, A., and Reed, G. L., 1996, Biochemistry 35:16879); in addition, the sequences at the C-terminal ends, especially before the last 30-32 residues of the native sequence (Kim. I. C., Kim, J. S., Lee, S. H., and Byun, S. M. 1996, Biochem. Mol. Bio. Int. 40:939. Lee, S. H., Jeong, S. T. Kim, I. C. and Byun S. M. 1997 Biochem. Mol. Bio. Int. 41:199. Fay, W. P., Bokka, L. V., 1998, Thromb. Haemost. 79;985) are important in generating the activator activity associated with the complex. Since a primary consideration in designing the SK-FBD chimeras was the the engineering of a decreased, or kinetically slowed, initial PG activation rate, we reasoned that either the C- or N-termini (or both, together) could be utilize to bear the FBDs in the hybrid structures, and that the presence of such extra domains in SK, either full-length or already truncated to the most functionally relevant regions of human fibronectin that can independently bind fibrin under physiological conditions (detailed earlier) and would also suitably retard and/or delay the PG activation rates observed normally with native SK and PG by interfering in the interactions of SK with PG to generate a functional activator complex. If the polypeptide in between these two distinct parts constituting the chamera were sufficiently flexible, proteolytic scission in this region would then result in the removal of the retarding/inhibiting portion (FBD component) from the SK-FBD hybrid and lead to a burst of PG activation after an initial delay. This proteolysis could be mediated by the amounts of endogenous plasmin generated in the vicinity of the pathological clot by intrinsic plasminogen activator/s of the system, such as TPA, urokinase etc already present in the circulatory system. Indeed, this premise was borne out by experimentation, which showed that the lag times of PG activation by the SK-FBD chimeras disclosed in this invention were directly governed by plasmin-mediated proteolysis of the hybrid proteins leading to the liberation

of the FBD portion from the SK-FBD followed by rapid PG activation by the SK. The direct implication of this functional property in a plasminogen activator is that once injected into the body, the protein could then traverse in an inactive state through the circulatory system and bind to the pathological clot by virtue of the fibrin affinity imparted by the fibrin binding domains thereby obviating or minimizing systemic PG activation. Thus, if the thrombolytic agent traverses the circulation prior to this activation (which is known to require 3-5 minutes in the human circulation), the fibrin affinity in the chimera would allow it to bind to the clot, thereby helping to localize the PG activation in and around the immediate vicinity of the thrombus.

At page 14 of the specification, please replace the figure legend for Fig. 24 with the following amended figure legend:

Fig. 24. Clot lysis by purified SK-FBD(4,5) chimeric protein in a plasma milieau. Figure 24 shows results with: closed triangles, 100 nm SK; open triangles, 50 nm SK; closed circles, 200 nm SK-FBD(4,5); closed squares, 100 nm SK-FBD(4,5); open squares, 50 nm SK-FBD(4,5).

The Examiner is authorized to remove the blank space at page 44 of the specification.

At page 60 of the specification, please replace the heading "CLAIMS:" with the following heading:

THE CLAIMS ARE: